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The Photoinduced Ring Expansion of Five Membered Ring Nitrites: A 1,6-*exo Ring Closure* Process of the Intermediate 5-Nitrosopentanoyl-type Radical.

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Abstract: The direct photolysis of cyclopentyl-type nitrites allows to detection, by EPR spectroscopy, the corresponding δ-valerolactam-1-oxyl type radical, owing to a ring expansion process as reported for steroidal 17-nitrites. For the formation of these radicals a 1,6 *exo ring closure* process of the intermediate 5-nitrosopentanoyl-type radical is involved. © 1997 Elsevier Science Ltd. All rights reserved.

Introduction

Ring expansion processes are well known in preparative organic chemistry[1] and among these a very interesting example was reported by Barton[2]; in fact by photolysing steroidal 17-nitrites he could obtain the corresponding hydroxamic acid as the only reaction product. Actually, the behaviour of the alkoxyl radicals deriving from the photolysis of the corresponding nitrite esters,[3] i.e. the intra and intermolecular H-abstraction[3] or, as for cycloalkyl nitrites, the C-C bond fission[4] reaction, was well documented but no evidence on a possible ring expansion process had been reported before. To account for the formation of the hydroxamic acids, the ring fission of the cyclopentoxyl type intermediate and then the rearrangement of the tertiary nitroso aldehyde, *via* a protolytic intramolecular substitution, was claimed. To support this mechanism, i.e. the role played by the molecular structure in the formation of a six-membered ring transition state, Kabasakalian[4] studied the behaviour to the photolysis of the cyclopentyl nitrite: this substrate led exclusively to the formation of the 5-nitrosopentanal, and that strengthened, as responsible of the non ring expansion process, the non favourable geometry. Furthermore, the same group of research and Nakazaki & Naemura[5] independently reported that the photolysis of the *d,l*-isobornyl and the *d,l*-bornyl nitrites led to the detection of the corresponding hydroxamic acid, the *dl*-1,8,8-Trimethyl-2-hydroxy-2-azabicyclo[3.2.1]octan-3-one, and they concluded that for these substrates the more rigid structure was providing the right geometry for the ring expansion process. However, results obtained in this laboratory on the photolysis of the cyclopentyl and cyclopentyl-type nitrites, by EPR spectroscopy, were suggesting that also simple alicyclic nitrites can undergo a steroid-type ring expansion process, and photochemical experiments at selected wavelengths shown that this process takes place *via* a 1,6-*exo* cyclization of the intermediate 5-nitrosopentanoyl-type radical.

Results and Discussion

As mentioned above, the only reported examples of non-steroid nitrites able to lead to the corresponding hydroxamic acid were the *d,l*-bornyl (**1**) and the *d,l*-isobornyl (**2**) nitrites, therefore experiments were conducted to investigate on the possible radical intermediates involved in the reaction mechanism. The photolysis within the cavity of an EPR spectrometer of a continuously flowed deoxygenated acetonitrile solution of (**1**) and (**2**), at different temperatures, was then performed: both substrates allowed to detect the *d,l*-1,8,8-Trimethyl-2-oxyl-2-aza-bicyclo[3.2.1] octan-3-one radical (**3**). The detection of such a radical can account for the formation of the parent hydroxamic acid and support the role played by the structure of the nitroso aldehyde intermediate in favouring the protolytic mechanism in accord with that reported in the literature. However, surprisingly, the isomeric *d,l*-1,8,8-Trimethyl-3-oxyl-3-aza-bicyclo[3.2.1] octan-2-one radical (**4**) was detectable too, Figure 1.

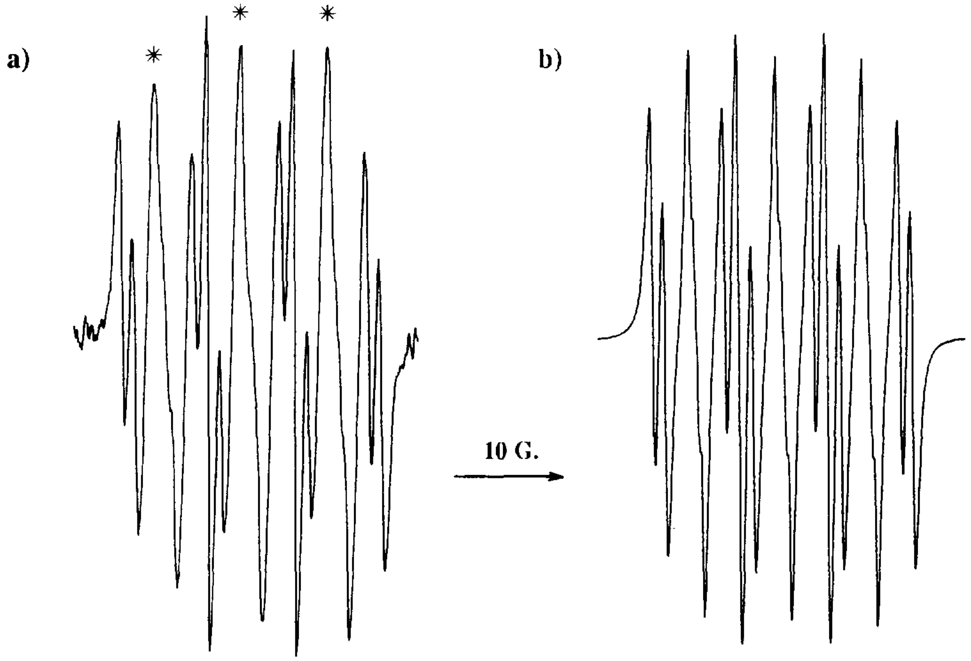
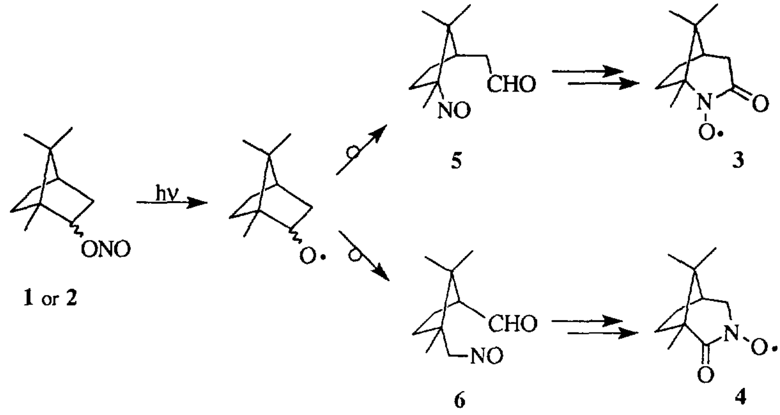


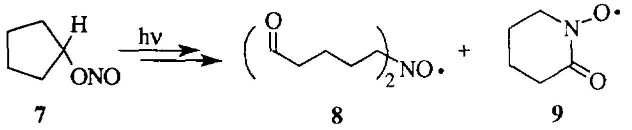
Figure 1. (**a**) EPR spectrum, at -35°C in AcCN, showing both radicals (3)* and (4). (**b**) Computer simulation with ratio between the radicals of 40:60.

To explain the formation of both radical species, the intermediate alkoxyl radical has to undergo two different β-scission processes leading respectively to the (2,2,3-Trimethyl-3-nitroso-cyclopentyl)-acetaldehyde (**5**), precursor of (**3**), and the 1,2,2-Trimethyl-3-nitrosomethyl-cyclopentanecarbaldehyde (**6**), precursor of (**4**), Scheme 1. However, since (**3**) and (**4**) have different structure could also be hypothesizable that not both can undergo a protolytic rearrangement.

SCHEME 1.

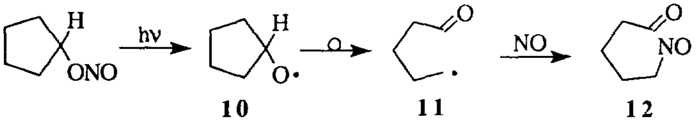


Nevertheless, to verify the role of the structure in the formation of the hydroxamic acid, it could be helpful to study the behaviour of the cyclopentyl nitrite (**7**) which leads to a nitroso aldehyde with no structural rigidity. When experiments were performed with this substrate, eq.1, two radical species were detected: the di-pentanal-5-yl nitroxide (**8**), and the δ-valerolactam-1-oxyl radical (**9**), (Figure 2), whose structure was confirmed by comparison with an authentic radical sample obtained by photolysis of the corresponding N-Nitroso δ-valerolactam in the presence of oxygen.[6]

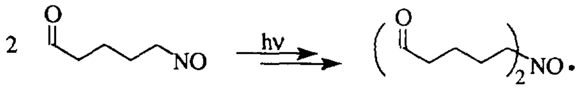


(1)

The formation of radical (**8**), as reported in the literature, can be accounted for *via* a photochemical reaction involving the 5-nitroso pentanal (**12**), eq.s 2 and 3;



(2)



(3)

for radical (9), the oxidation of the parent hydroxamic acid formed *via* a protolytic rearrangement of (12) could be implied, although never detected among the reaction products.

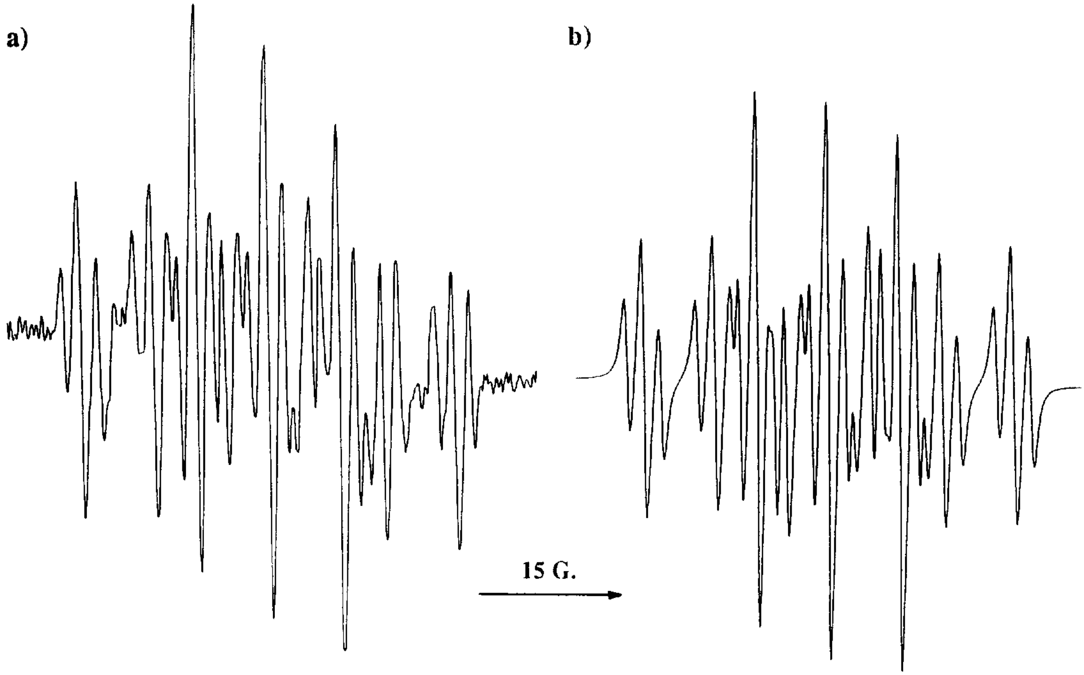
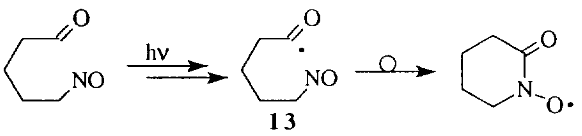


Figure 2. (a) EPR spectrum of radical (9), recorded between -50°C and +25°C. (b) Computer simulated.

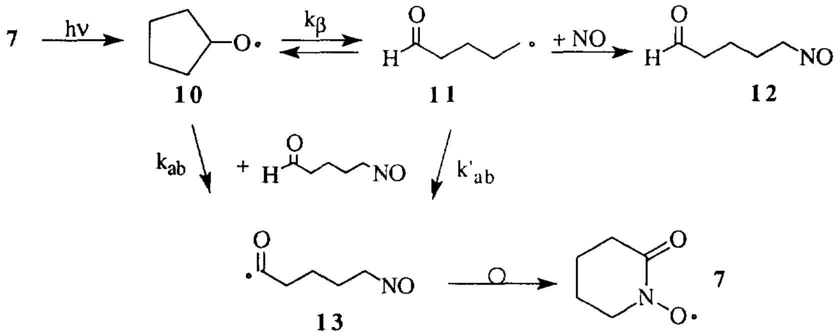
Actually, the presence of (9) was yielding evidence against the hypothesis that the intermediate nitroso aldehyde requested a rigid structure to undergo a possible rearrangement, therefore a different mechanism could be hypothesised. According to Mackor's results[8], who reported the possibility to generate an acyl alkyl nitroxide through the photoinduced reaction between a nitroso alkane and an aldehyde, the following reaction mechanism could be taken into account, eq.4.



(4)

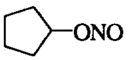
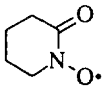
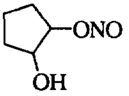
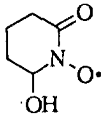
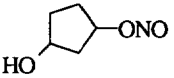
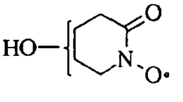
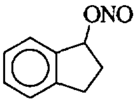
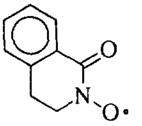
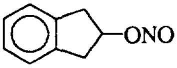
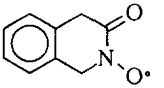
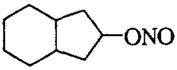
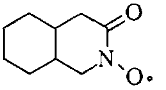
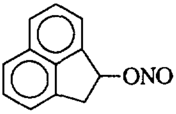
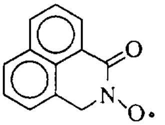
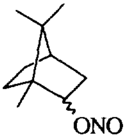
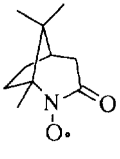
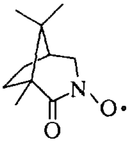
In fact, the main product of the photolysis of the cyclopentyl nitrite, the 5-nitroso pentanal, contains both groups, CHO and NO, involved in the Mackor-type reaction, and the acyl radical (13), precursor of (9), could be produced *via* abstraction of the aldehydic hydrogen of the 5-nitrosopentanal by CO and/or NO in their excited state. However, because the photochemical experiments had been conducted with the full mercury arc, both groups could be excited at once and act as H-abstractors, thus, to clarify their role, experiments with selected energies were performed. As reported in the literature,[9] nitroso alkanes show absorption due to the NO group in the red ($\lambda_{max} \approx 680$ nm) and in the ultraviolet ($\lambda_{max} \approx 260$ nm) regions, and the possible ways of decay of these excited states are the C-NO bond cleavage and/or the H-abstraction process from the medium. The aldehydic carbonyl acts as H-abstractor when excited at $\lambda_{max} \approx 290$ nm, whilst the cyclopentyl nitrite undergoes the O-NO bond cleavage when photolised with wavelengths in the $320 \leq \lambda \leq 420$ nm region. Therefore, three different experiments with filtered light were performed. The first was conducted using a glass filter which transmitted wavelengths greater than 320 nm, and radical (**9**) was the only detectable species. With filters transmitting wavelengths lower than 420 nm and in the $320 \leq \lambda \leq 420$ nm region, radicals (**8**) and (**9**), and (**9**) were respectively detectable. If the first two experiments could induce to consider both groups involved in the H-abstraction process, the latest unequivocally supported, for the formation of (**9**), the involvement of radical species, acting as H-abstractors, directly achievable from the O-NO bond cleavage, and not the CO and/or NO groups in their excited state. In the light of this result it can be hypothesised that both the cyclopentoxyl radical (**10**), obtained from the primary photochemical process which (**7**) undergoes, and the pentanal-5-yl radical (**11**), deriving from its β-scission, could perform such a reaction. Scheme 2.

SCHEME 2.



Actually, the β-scission process is usually reported to occur more rapidly then the competing processes as H-abstraction or disproportionation, but Beckwith[10] has recently demonstrated its reversibility and, in certain conditions, the possibility for the competing H-abstraction process to take place faster. In particular, the 5-nitroso pentanal[11] (**12**), can act as a selective H-donor resulting in the trapping of (**10**) in the preference of (**11**), and that supported by the fact that the alkoxyl radicals generally undertake H-abstraction from organic substrates with rate constants $\geq 10^3$ time larger than those of alkyl radicals ($k_{ab} \gg k'_{ab}$); moreover, aldehydes are known to be good H-donors since they have weak aldehydic C-H bond.

Table 1. Hyperfine Splitting Constants of δ-valerolactam-1-oxyl type Radicals.

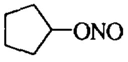
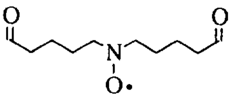
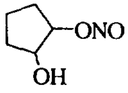
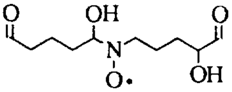
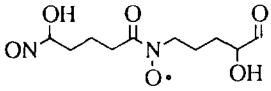
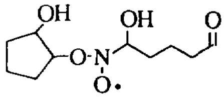
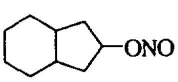
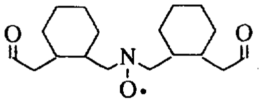
Substrate	Radical	h.f.c. (Gauss)
		$a_N = 7.60$ $a_{2H(6)} = 11.60$ $a_{2H(3)} = 1.80$
		$a_N = 7.08$ $a_{H(6)} = 7.08$ $a_{2H(3)} = 1.75$
		$a_N = 7.25$ $a_{H(6)} = 10.62$ $a_{H(6')} = 12.62$ $a_{H(3)} = 1.50$ $a_{H(3')} = 2.13$
		$a_N = 7.25$ $a_{2H(8)} = 10.00$
		$a_N = 7.13$ $a_{2H(8)} = 11.60$ $a_{2H(3)} = 1.80$
		$a_N = 7.25$ $a_{2H(10)} = 11.75$ $a_{2H(3)} = 1.87$
		$a_N = 7.13$ $a_{2H(9)} = 13.25$
		$a_N = 7.50$ $a_{H(4)} = 0.45$ $a_{H(4')} = 0.80$
		$a_N = 7.62$ $a_{H(4)} = 6.25$ $a_{H(4')} = 11.25$

The g-values, 2.0064±0.0001, have been calculated by comparison with the DPPH g-value (2.0037).

Furthermore, the kinetic data reported[9] for these reactions allow to evaluate the relative rate constants between the two processes which (**10**) can undergo and in particular at 250°K, temperature at which the experiments are usually conducted, the rate ratio results to be $K_{ab}/K_{\beta} \approx 1.1\ M^{-1}$ (Scheme 2). Thus, the intermediate 5-nitrosopentanoyl radical (**13**), obtained through the H-abstraction from (**12**) by (**10**), *via* a 1,6 exo-cyclization leads to radical (**9**).

However, it needed to verify if this behaviour was restricted just to the nitrites (7), (**1**) and (**2**) or, in general, cyclopentyl-type nitrites were undergoing such a ring expansion process. Several substrates were then investigated and all allowed to detect the corresponding δ-valerolactam-1-oxyl type radical, Table 1. Experiments were then conducted with selected wavelengths and these confirmed the role of the 5-nitrosopentanoyl-type radical intermediate responsible of the 1,6 *exo ring closure* process, as proved for the cyclopentyl nitrite. With some substrates, Table 2, other nitroxides were detectable which confirmed the formation of the intermediate nitroso aldehyde.

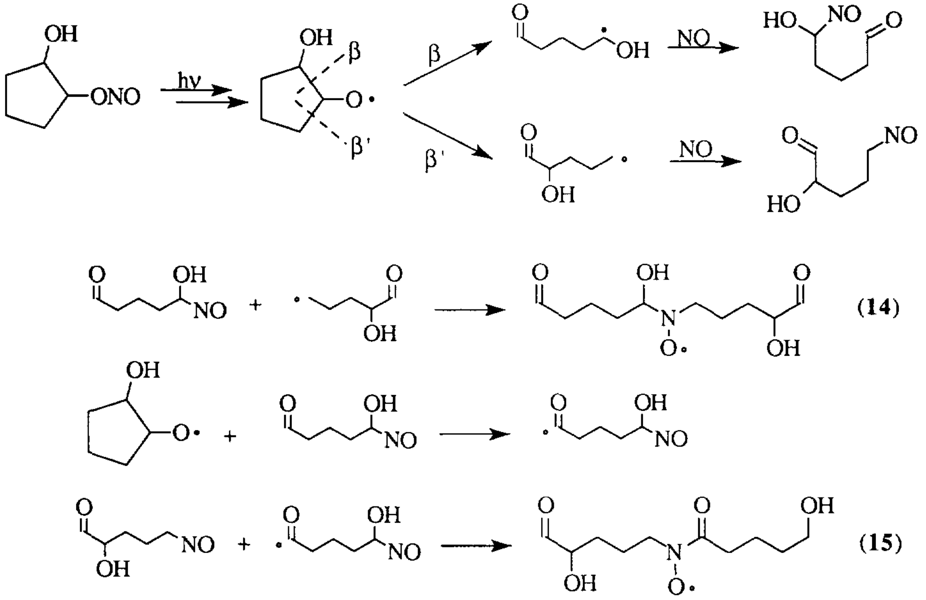
Table 2. Hyperfine Splitting Constants of Linear Nitroxides[a] in Gauss.

Substrate	**Nitroxides**		
	(**8**)  a_N = 15.00 a_H (4H) = 10.00 g = 2.0054		
	(14)  a_N = 14.31 a_H (2H) = 8.76 g = 2.0054 a_H = 5.38	(15)  a_N = 7.63 a_H (2H) = 6.50 g = 2.0065	(16)  a_N = 27.25 a_H = 2.75 g = 2.0053
	 a_N = 15.00 a_H (4H) = 10.00 g = 2.0053		

a) The g-values have been calculated by comparison with the DPPH g-value (2.0037).

In particular the 2-hydroxy-cyclopentyl nitrite allowed to detect, besides the 6-hydroxy-δ-valerolactam-1-oxyl radical three more radical species. To account for these species it was necessary to consider the involvement of two different β-cleavages of the alkoxyl intermediate: one leading to the 5-nitroso-5-hydroxypentanal, precursor of the 6-hydroxy-δ-valerolactam-1-oxyl radical, and one to the 5-nitroso-2-hydroxypentanal. In fact, two of the detected radical species show a structure which can be accounted for only by the involvement of both the nitroso aldehyde intermediates; the radical (**14**) can in fact be formed by trapping of the 2-hydroxypentanal-5-yl radical by the 5-hydroxy-5-nitrosopentanal and radical (**15**) by trapping of the 5-hydroxy-5nitrosopentanoyl radical by the 2-hydroxy-5-nitrosopentanal, as reported in Scheme 3.

SCHEME 3.



The third species, the alkyl alkoxy nitroxide (**16**), could be accounted for, as usually reported in the literature, by the reaction of the 2-hydroxypentoxyl radical and the 5-hydroxy-5-nitrosopentanal, however evidence suggest, for its formation, a different reaction mechanism which will be discussed in a following paper.

Experimental

Material. - The alicyclic nitrites were prepared according to the general method by esterification of the corresponding alcohols with nitrous acid at 0°C and were vacuum distilled before use. Each of the light-yellow distilled oils was identified and the purity controlled by GC-Mass spectroscopy. The N-Nitroso-δ-valerolactam was prepared in accordance with the method reported by Huisgen & Reinertshofer.[6] All the starting alcohols were commercial products except the β-Hydrindanol, $C_9H_{16}O$, which was prepared according to the procedure of Huckel *et al.*[12] *via* reduction of the corresponding Hydrindanone. The acetonitrile (99.9+%, HPLC grade) was obtained from Aldrich.

Photolysis apparatus. - Irradiation was performed with an OSRAM HBO 500W/2 high pressure mercury lamp provided with CORNING glass coloured filters. The CORNING glass filter number 0160(0-54) was used for the experiments at $\lambda \geq 320$ nm and the filter number 9863(7-54) for those at $\lambda \leq 420$ nm; a combination of the two was used for the experiments at $320 \leq \lambda \leq 420$ nm.

Spectroscopic measurements.- The U.V.-visible absorption spectrum of nitrites in acetonitrile were recorded using a Perkin-Elmer spectrometer. GC-MS analysis were carried out with a Carlo Erba QMD 1000 instrument. ESR spectra were recorded on Varian E-104 X-band spectrometer with a 100 KHz modulation and the dynamic ESR experiments were performed using a 50 ml gastight SGE syringe driven by a INFORS Precidor.

ESR Experiments.- The solutions of cycloalkyl nitrites, in acetonitrile, were photolysed within the cavity of the ESR spectrometer equipped with a variable temperature control system; the solution was flowed in the cavity through a flat cell arrangement (0.3 mm. cell width) and the flow was ranging between 0.1 and 0.6 ml/min. The solutions were deareated prior to use by purging with N_2-gas for 50-60 min.. The light was focused onto the sample by an elliptical mirror and two quartz lenses. The g-value for the radical species were determined by comparison with g-value (2.0037) of DPPH.

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11. Its formation occurs through a quite efficient reaction between radical (**11**) and free NO, in fact the 5-nitroso pentanal dimer is the main reaction product.[4] Furthermore, the efficiency of such a reaction can also account for the non detection of radical (**8**) in the 320 $\leq\lambda\leq$ 420 nm experiment because of the low concentration of free (**11**); on the contrary its detection in the experiment with the UV light induce to consider the cleavage of the C-NO bond of (**12**) as source of free (**11**).

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